UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,987	04/20/2001	Ronald S. Chamberlain	2026-4231US3	2855

7590 03/14/2002

MORGAN & FINNEGAN, L.L.P.
345 Park Avenue
New York, NY 10154-0053

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,987	CHAMBERLAIN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Specification

The specification does not describe Fig. 1B-1E (page 5).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of enhancing a CTL response in a mammal comprising administering a vaccinia viral vector encoding an antigen operably linked to a promoter followed by administering a fowlpox vector encoding said antigen operably linked to a promoter such that an enhanced CTL response against said antigen occurs as compared to vaccinia followed by vaccinia, fowlpox followed by fowlpox or fowlpox followed by vaccinia, does not reasonably provide enablement for obtaining an enhanced immune response using any combination of vectors as broadly claimed or treating cancer as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-8 do not have an enabled use as written because they merely require enhancing an immune response in a mammal. The only disclosed purpose for enhancing an immune

response in a mammal using vectors encoding antigens is to treat cancer, infectious disease or autoimmune disease (page 4, lines 2-13). Merely enhancing an immune response does not have a disclosed use that is enabled. In particular, claim 5 does not have an enabled use as written because inducing an immune response using a vector encoding an antigen and an immunostimulatory molecule is only disclosed for treating cancer. If other enabled uses for merely inducing an immune response in a mammal using vectors are disclosed, please point to such by page and line number.

It was known in the art that an enhanced CTL response against an antigen could be induced upon administering wild-type vaccinia followed by a fowlpox vector encoding an antigen (Wang, 1995, J. Immunol., Vol. 154, pages 4685-4692). Administering wild-type fowlpox followed by vaccinia virus encoding an antigen did not provide an enhanced CTL response because fowlpox followed by fowlpox encoding an antigen did not have a suppressed CTL response (page 4689, col. 2).

The specification demonstrates administering a vaccinia, fowlpox or plasmid vector encoding an antigen followed by a different boosting vector encoding the antigen enhanced the CTL response against the antigen as compared to vaccinia followed by vaccinia or fowlpox followed by fowlpox (page 25, Ex. 2). However, administering vaccinia, fowlpox or plasmid vector encoding an antigen followed by a different boosting vector encoding the antigen enhanced the antibody response against the antigen only under certain conditions. For example, plasmid followed by plasmid worked better than plasmid followed by vaccinia or fowlpox.

Vaccinia followed by plasmid or fowlpox were both better than vaccinia followed by vaccinia. Fowlpox followed by plasmid was better than fowlpox followed by fowlpox, but fowlpox followed by vaccinia was not. Thus, only particular combinations of vectors enhanced the immune response. The combination of vectors required to enhance the immune response depends upon the immune response being monitored. The specification does not provide adequate guidance indicating adenovirus or any other vector as broadly claimed would enhance the immune response in a mammal in combination with a different vector. Given the state of the art taken with the guidance provided in the specification, it would require one of skill undue experimentation to determine the combination of vectors as broadly claimed that enhance the immune response against antigen. Therefore, the claims are not enabled as broadly written for enhancing an immune response using any combination of vectors as broadly claimed.

Claims 9-20, directed toward treating cancer, are not enabled because the specification does not provide adequate guidance to treat cancer using vectors encoding antigens as claimed.

The state of the art at the time of filing was that the combination of vector, promoter, antigen, target tissue, level of expression and route of administration required to target the desired tissue and obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) reviewed vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into

components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicated one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed new techniques under experimentation in the art which showed promise but stated such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviewed vectors known in the art for use in gene therapy and discussed problems associated with each type of vector. The teachings of Verma indicated a resolution to vector targeting has not been achieved in the art (see entire article). Verma also taught appropriate regulatory elements may improve expression, but it was unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviewed various vectors known in the art and indicated that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus, the state of the art at the time of filing was that it was unpredictable how to treat cancer using a vector encoding an antigen as claimed.

The specification discusses various viral vectors (pages 9-10) and various antigens (pages 11-13) to treat a variety of diseases including cancer (page 11, lines 11-35). Example 1 teaches increasing survival of mice having β-gal-expressing tumors using vaccinia followed by fowlpox

or fowlpox followed by vaccinia, each of which encode β-gal (page 21; Fig.1) and contemplates administering vectors encoding tumor associated antigens (TAA) against melanoma (example 5). The specification does not provide adequate guidance to treat cancer as claimed because the β-gal tumors do not correlate to tumors having tumor associated antigens. β-gal does not correlate to any TAA because it is a foreign protein while TAAs are self-proteins, because β-gal and TAAs known in the art do not have the same epitopes recognized by the immune system, β-gal and TAA have different MHC restriction and because β-gal and TAAs ability to induce immunity differ. Specifically, the specification does not provide any guidance to treat cancer using MART-1, gp100, TRP-1 or TRP-2 because the specification does not correlate the epitope of β-gal is the same amino acid sequence and structure as epitopes of MART-1, gp100, TRP-1 or TRP-2, that MART-1, gp100, TRP-1 or TRP-2 are H-2L^{d} -restricted, or that MART-1, gp100, TRP-1 or TRP-2 induce an equivalent immune response as β-gal.

Thus, the specification does not provide adequate guidance for one of skill to administer a vector to a mammal and treat cancer by teaching the level of expression of antigen required to induce the desired immune response, how to target antigen expression to the desired tissue such that the desired immune response is obtained, or by correlating β-gal to tumor antigens such as MART-1, gp100, TRP-1 or TRP-2. Given the state of the art at the time of filing taken with the teachings in the specification, it would require one of skill undue experimentation to determine the dosage, route of administration, vector, promoter, antigens, target tissue or level of antigen expression required to obtain the desired immune response and treat cancer as claimed.

The specification does not enable using vectors encoding antigens and immunostimulatory molecules such as a cytokine, growth factor or a co-stimulatory molecule to treat cancer. Vieweg (1995, Cancer Investigation, Vol. 13, pages 193-201) taught it was unpredictable what combination of cytokine was required for what tumor (page 198, column 1, line 1). The specification fails to enable using such a vector to treat cancer by teaching the level of expression required, how to obtain the desired level of expression using gene therapy or the combination of cytokine to use with an antigen to treat cancer.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the metes and bounds of an "enhanced immunological response" cannot be determined. It cannot be determined if the response is enhanced as compared to not administering the two vectors, as compared to administering two of the same vectors or some other parameter.

Claims 1 and 9 are indefinite because the phrase "heterologous boosting immunization" is unclear. It is unclear if the term "heterologous" indicates the vectors are foreign to the mammal, if the vectors are different than each other or if the vectors have different effects on the immune

system. It is unclear if "boosting" occurs when both vectors are administered or only after administration of the second vector.

Claim 1 is indefinite because "genes" do not necessarily encode "antigens." Antigens may be nine amino acids in length; therefore, nucleic acids encoding antigens do not necessarily constitute a gene. It is unclear if the nucleic acid sequence encoding an antigen is limited to only those in the context of an entire gene.

Claims 5 and 14 are indefinite because it is unclear how the immunostimulatory molecule further limits the claims. The vector in parent claims 1 and 9 encode an antigen and may encode viral proteins, both of which are immunostimulatory. It is unclear if "immunostimulatory molecules" are limited to cytokines and co-stimulatory molecules or if the term encompasses antigens and viral proteins.

Claims 5 and 14 are indefinite because genes do not encode any "immunostimulatory molecule" as claimed. Molecules that are not proteins may be immunostimulatory, e.g. phenol, but cannot be encoded by a gene. The word "molecule" should be changed to "protein" to be clear.

Claim 9 is indefinite because mere administration of two vectors encoding antigen is not "treating said patient" as claimed. As written, the claim does not require the mammal have a tumor expressing the antigen found in the vectors or any therapeutic effect, e.g. a reduction in tumor burden. Therefore, the claims are unclear because they are missing essential elements - a

mammal having a tumor expressing the antigen encoded by the vectors and obtaining a therapeutic effect.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 1-3, 5-7, 9, 14-16, 18 and 19 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Chamberlain et al. (April 20-24, 1996, Proc. Ann. Meeting American Assoc. Cancer Res, Vol. 37, abstract 3263).

Chamberlain taught administering a vaccinia virus encoding β-gal to mice followed by fowlpox virus encoding β-gal and obtaining an increased CTL and antibody response (see entire abstract). Chamberlain also taught administering fowlpox virus followed by vaccinia virus. Claims 5 and 14 are included because viral vectors encodes viral proteins that are immunostimulatory and because β-gal is an immunostimulatory molecule. Claims 9, 14-16, 18 and 19 are included because the mere administration of two vectors is "treatment" as claimed; claims 9, 14-16, 18 and 19 do not require any therapeutic effect. The publication date of the abstracts from the proceedings of the meeting was March 21, 1996 which precedes the effective

filing date of the instant application which is April 22, 1996. Thus, Chamberlain anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 5-7, 9, 14-16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92).

Wang taught administering a wild-type vaccinia virus to mice followed by administering a fowlpox virus encoding β-gal which caused an increase in CTL response in splenocytes as compared to administering wild-type vaccinia followed by vaccinia encoding β-gal (page 4689, col. 2, Fig. 6, 1st full para.). Wang did not teach administering vaccinia virus encoding β-gal followed by administering fowlpox virus encoding β-gal. However, Wang taught a vaccinia virus encoding β-gal. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to pre-immunize with vaccinia encoding β-gal followed by fowlpox encoding β-gal as taught by Wang. One of ordinary skill in the art at the time the invention was made to replace wild-type vaccinia with vaccinia encoding β-gal to introduce the DNA encoding the antigen sooner while pre-immunizing.

Similarly, Wang taught administering a wild-type fowlpox followed by vaccinia encoding β-gal which also caused an immune response (page 4689, col. 2, 1st para.). Wang did not teach pre-immunizing with fowlpox encoding β-gal followed by vaccinia encoding β-gal. However, Wang taught administering fowlpox virus encoding β-gal caused an immune response. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to pre-immunize with fowlpox encoding β-gal followed by vaccinia encoding β-gal. One of ordinary skill in the art at the time the invention was made to replace wild-type fowlpox with fowlpox encoding β-gal to introduce the DNA encoding the antigen sooner while pre-immunizing.

Claim 5 is included because vaccine virus encodes proteins that are immunostimulatory and because β-gal is an immunostimulatory molecule. Claims 9, 15 and 19 are included because the mere administration of two vectors is "treatment" as claimed; claim 9, 15 and 19 do not require any therapeutic effect.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

5. Claims 1-3, 5-7, 9-11, 14-16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92).

Wang taught administering vaccinia encoding β-gal to mice followed by administering fowlpox encoding β-gal or vice versa which caused an immune response (see 103 rejection above). Wang did not expressly teach performing the method wherein β-gal is replaced with

MART-1 or gp100. However, Wang suggested replacing β-gal with MART-1 and gp100 and taught making fowlpox virus encoding MART-1 and gp100 (page 4690, col. 2, last 2 para.). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the β-gal gene is replaced with MART-1 or gp100 as suggested by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with MART-1 or gp100 to determine if self proteins such as MART-1 or gp100 induced the same immune response as a foreign protein (β-gal) and to determine if MART-1 or gp100 enhanced the precursor frequency of T-cells that recognize MART-1 or gp100 prior to *ex vivo* expansion (page 4690, col. 2, para. 2, line 4).

Wang did not expressly teach performing the method wherein the vectors encode an immunostimulatory molecule. However, Wang taught adding a nucleic acid sequence encoding IL-2, IL-12, GM-CSF, et al. to the vectors encoding tumor antigens (page 4690, col. 2, 8 lines from the bottom). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein a nucleic acid sequence encoding an immunostimulatory molecule is added to the vectors encoding antigen. One of ordinary skill in the art at the time the invention was made would have been motivated to add a cytokine to the vectors at the suggestion of Wang.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

6. Claims 1-3, 5-7, 9, 12-16, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Orlow (1995, PNAS, Vol. 92, pages 10152-10156).

Wang taught administering a vaccinia encoding β-gal, MART-1 or gp100 to mice followed by administering a fowlpox encoding β-gal, MART-1 or gp100 which caused an immune response against the antigen. Wang did not teach the method wherein the antigen is TRP-1 or TRP-2. However, Orlow taught the nucleic acid sequence of TRP-1 and TRP-2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the antigen was TRP-1 or 2 as taught by Orlow. One of ordinary skill in the art at the time the invention was made would have been motivated to replace MART-1 or gp100 with TRP-1 or 2 because MART-1, gp100, TRP-1 and 2 are all melanoma antigens. One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with TRP-1 or 2 to determine if self proteins such as TRP-1 or 2 induced the same immune response as a foreign protein (β-gal). One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with TRP-1 or 2 to determine the precursor frequency of T-cells that recognize TRP-1 or 2 *in vivo*.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

7. Claim 1-9, 14-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Zhai (Jan. 15, 1996, J. Immunol., Vol. 156, No. 2, pages 700-710).

Wang taught administering a vaccinia virus encoding β-gal to a mice followed by administering a fowlpox virus encoding β-gal which caused an increase in CTL response in splencytes as compared to administering two doses of vaccinia virus encoding β-gal. Wang did not teach replacing the vaccinia virus or fowlpox virus with an adenovirus. However, Zhai taught administering an adenoviral vector encoding β-gal to mice and obtaining an immune response.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the vaccinia virus or fowlpox virus was replaced with the adenoviral vector taught by Zhai. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the vaccinia virus (the first vector) with the adenoviral vector to increase the CTL response against antigen as compared to administering adenoviral vector followed by readministration of adenoviral vector. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the fowlpox virus (the second vector) with the adenoviral vector to determine if fowlpox was the only virus that could be used to obtain a CTL response against antigen after administering vaccinia virus.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER